SUMMER 2014

UTHealth
The University of Texas Health Science Center at Houston
Medical School

CNRA Connections

Center for Neurobehavioral Research on Addiction

Department of Psychiatry

Science & Electronic Cigarettes: Smoke and Mirrors

Michael Weaver, MD

Electronic cigarettes (ECs), also referred to as "e-cigarettes," consist of a power source (battery) and heating element (atomizer) that vaporizes a solution (e-liquid), which the user inhales. E-liquids contain propylene glycol and/or vegetable glycerin, flavorings, and usually—but not always—nicotine.

ECs have the potential to deliver nicotine and address behaviors associated with smoking–such as hand-to-mouth movement–so, theoretically, they could be a useful quit method. Many EC users surveyed do use ECs to quit smoking or to reduce use of tobacco cigarettes.

However, surveys may be biased, as they recruit from websites frequented by EC enthusiasts, and results are based on self-report. Only five studies have assessed whether ECs can help tobacco smokers quit, and only two were randomized trials. Some participants did quit smoking completely: 11% at 12 weeks and 9% at one year.

ECs are a different system of nicotine replacement than FDA-approved smoking cessation aids such as nicotine patches, gum, or lozenges. ECs are not FDA-approved and are presently unregulated.

Patients who use approved medications to quit smoking have

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Inside This Issue

Newsletter layout and design by Kathryn Tipton

Harnessing Technology To Study Real Life Cocaine Effects

Jin Yoon, PhD

Novel methods for tracking cocaine use in the natural environment are sorely needed. An estimated 1.5% of Americans report current cocaine use, putting themselves at increased risk for a host of adverse health consequences. Cocaine use is responsible for over 40%, or nearly half a million, annual Emergency Department visits related to illicit drug use. Additionally, cocaine use is linked to other major medical complications related to overdose, premature death, crime, drug-exposed neonates, and infectious diseases such as HIV.

Currently, there are no FDA-approved medications for cocaine use, despite numerous clinical trials testing a wide range of promising compounds.

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CNRA: About us

MISSION:

To develop evidence-based treatment for substance use disorders (SUDs) using decisions informed by behavioral neurosciences.

AIMS:

In pursuit of this mission the CNRA aims to:

- Map out the neurological, behavioral, and clinical mechanisms that contribute to drug addiction
- Target key mechanistic processes in the development of SUD treatment
- Evaluate treatment efficacy using innovative clinical trial designs and statistical methods

Core Faculty:

Prashant Gajwani, M.D.

Charles Green, Ph.D.

Scott Lane, Ph.D.

Joy Schmitz, Ph.D.

Anka Vujanovic, Ph.D.

Margaret Wardle, Ph.D.

Michael Weaver, M.D.

Jin Yoon, Ph.D.

Interested in research?

Contact us!

(713) 486-2823

Rolanda Johnson
CNRA Program Manager

Director's Message

Joy Schmitz, Ph.D.

Among many recent developments, this issue of *CNRA Connections* highlights the addition of two CNRA faculty members. **Dr. Michael Weaver** joined the group in January as the new Medical Director and **Dr. Margaret Wardle** arrived in February as Assistant Professor and new investigator of a NIDA B/START award.

With our team getting bigger and more visible, we developed a new CNRA logo to identify ourselves when communicating and disseminating our work. At the annual meeting of the College for Problems of Drug Dependence (CPDD) later this month, six presentations from CNRA scientists will display our new logo, shown below. Huge thanks to **Dr. Jin Yoon** for volunteering his design talent.

This spring, I was appointed the Faillace Endowed Professorship, established in 2011 by **Cynthia and Ray Wright** in honor of **Louis A. Faillace, M.D.**, the first chairman of the Department of Psychiatry at the University of Texas Health Science Center at Houston.

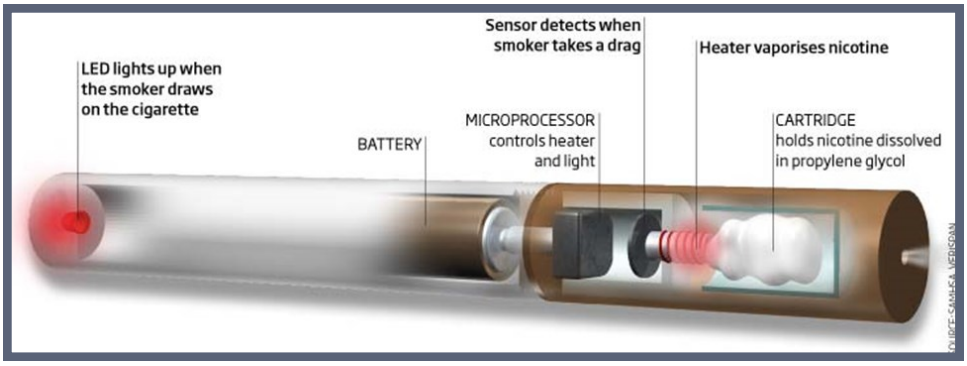
The professorship supports excellence in psychiatric research and patient care, and envelops the mission of the CRNA – to develop evidence-based addiction treatment. Funds provided by grateful and generous donors such as Mr. and Mrs. Wright make it possible to promote and support new research and provide research opportunities for trainees.

CNRA
CENTER FOR NEUROBEHAVIORAL RESEARCH ON ADDICTION

CNRA Faculty and Staff

Science and Electronic Cigarettes, continued from page 1

access to behavioral programs that are funded by the manufacturer. However, EC manufacturers do not provide any funding for behavioral cessation programs, and have a financial incentive for patients to be unsuccessful at cessation. Without the behavioral component, success rates may be lower. Whether or not ECs can help tobacco smokers quit smoking is still unclear.



An electronic cigarette may look like a tobacco cigarette, but contains flavored nicotine liquid released as hot vapor that is inhaled, called "vaping."

People who have quit smoking cigarettes may relapse to nicotine addiction after using electronic cigarettes.

Nicotine exposure changes nicotine receptors in the reward centers of the brain, which increases the potential for development of tobacco use disorder (TUD) and facilitates escalating from occasional to regular use, including the leap to daily cigarette smoking. Data from a study with which I was involved suggest that ECs have a lower abuse potential than tobacco cigarettes; however, there is still potential to develop a TUD from regular use of ECs. Even people who have quit smoking cigarettes may relapse to nicotine addiction after using ECs.

Contrary to cigarette use patterns, a recent study revealed that *higher* levels of education are associated with EC use–a finding that suggests ECs may even have the capacity to reverse the previous trend of tobacco use denormalization in this group. Users may also tamper with the EC to provide larger doses of nicotine, or make changes to the e-liquid.

Electronic cigarettes should not be considered safe because nicotine itself has long-term consequences.

The use of ECs may result in exposure to carcinogens, pollen, and byproducts of vaporization such as formaldehyde. Cartridge refills also may contain impurities. A recent study showed that 10 of 20 e-liquids analyzed contained up to five times the maximum allowed levels of impurities. Currently no country regulates EC as medications or drug delivery devices. Therefore, there are no manufacturing standards and no monitoring of labeling accuracy, or presence of impurities or toxic compounds.

ECs are a potential form of harm reduction for those who use other tobacco products, due to reduced exposure to known carcinogens and other toxic compounds found in tobacco products. When used as a form of medication therapy for tobacco cessation ECs may reduce harm if the tobacco user quits successfully. However, ECs should not be considered safe because nicotine itself has long-term consequences; ECs contain impurities; and use of nicotine leads to addiction, which can have serious consequences.

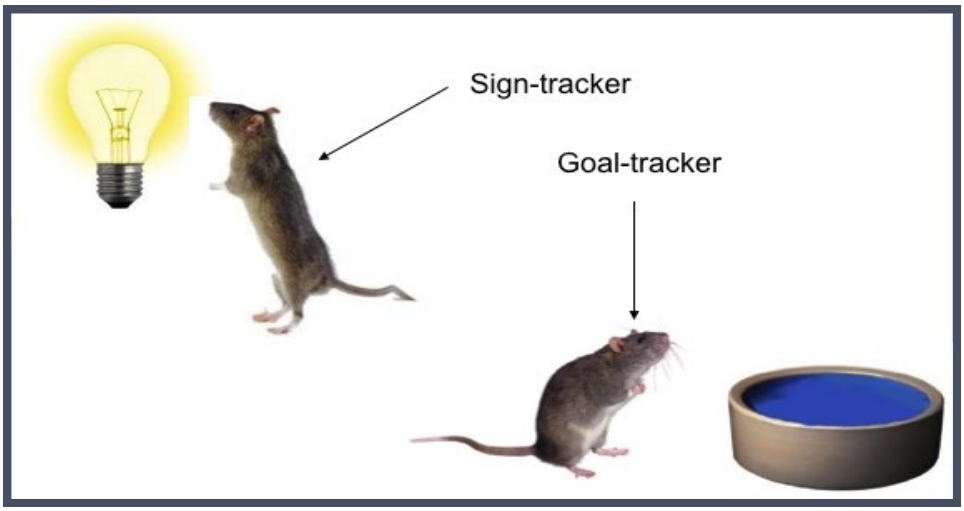
Smoking in the USA

Cigarette smoking continues to be the leading cause of preventable disease and death in the United States, accounting for approximately 443,000 deaths annually. Almost 1 in 5 Americans are still smokers.

Signs of Temptation: Sign-Tracking in Humans

Margaret Wardle, PhD

A central question of addiction research is who becomes addicted and why. Recent studies in rodents indicate there are fundamental differences in the way certain individuals respond to cues (i.e. sights, smells or objects) associated with reward that may put those individuals at risk for addiction. CNRA researchers will be the first to apply these findings to studying addiction risk in humans.



Sign-tracking rats approach cues that signal reward while goal-tracking rats approach the actual reward.

Responses to reward cues can be divided into two broad categories. For some rats, the reward cue -- usually a light or lever presented right before food delivery -- is merely a signal that reward is coming. When presented with a cue, these animals go to where the reward is usually delivered and wait- like a dog waiting by a food bowl. This behavior is called "goal-tracking," because the animal goes to the goal, or reward. By contrast, for other rats, the cue itself seems to become desirable and attractive. This subset of animals will approach the cue, or "sign," associated with reward, and will lick, touch and treat the cue as if it were food. This behavior is called sign-tracking. Sign-tracking can be such a strong compulsion that animals will engage in it even when approaching the cue results in the reward being withheld.

Importantly, sign-tracking animals appear "at risk" for drug use. They take drugs more readily, and are more likely to relapse to drug-seeking in the presence of drug-associated cues. Further, sign-tracking is a consistent individual trait -- animals who sign-track today will also sign-track tomorrow, and animals that sign-track to one reward, like food, will also sign-track to another, such as drugs.

Sign tracking may represent an underlying individual difference in brain functioning that makes certain individuals vulnerable to addiction.

Sign-tracking also appears to be heritable. Researchers working with rodents have traced these differences in behavior to fundamental differences in the brain's dopamine system. This system is involved in signaling "natural" rewards, and is also strongly affected in addiction. Specifically, in sign-trackers the sight of a cue triggers a burst of dopamine in the nucleus accumbens, a "reward center" in the brain, while in goal trackers it does not. Interestingly, this pattern of activation is very similar to that which occurs when an addicted individual is presented with a drug-related cue. Putting this evidence together, sign-tracking may represent an underlying individual difference in brain functioning that makes certain individuals vulnerable to addiction.

This individual difference may contribute to addiction in humans by resulting in more "temptation" or approach behavior when individuals see cues associated with a drug, such as passing by a bar. The first step in confirming this hypothesis is simply to develop a measure of sign-tracking in humans. This step is currently underway at the CNRA, funded by a grant from the National Institute on Drug Abuse (R03 DA036649; PI: Wardle). To

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Signs of Temptation, continued from page 4

keep the measure as parallel as possible with animal studies, young healthy volunteers will undergo a conditioning procedure in which food is repeatedly paired with "neutral" pictures. Because humans do not generally lick or gnaw on reward cues, subtle measures of positive orientation and approach will be used to gauge the degree of attraction to the pictures after conditioning. These include micro-movements in facial muscles associated with smiling, and direction of eye-gaze to cues, among others.

Sign tracking could predict who is at risk for drug use prior to any exposure to drugs at all.

These measures should allow identification of a sub-set of people who are particularly attracted to cues, i.e. human sign-trackers. Once a measure of human sign-tracking is developed, there will be many potential applications. Such a measure could predict who is at risk for drug use prior to any exposure to drugs at all, and could distinguish which addicted individuals are at the greatest risk for relapse in the presence of cues, allowing interventions for relapse prevention to be tailored to the individual.

This exciting project could lead to a host of future studies elucidating the role of sign-tracking in addiction in humans, and applying these findings to addiction prevention and treatment.

Harnessing Technology, continued from page 1

However, treatment outcome is commonly measured by assessing cocaine positive or negative urine samples. Such a measure may not capture potentially important clinical benefits associated with changes in cocaine use.

BioHarness RPM device

A promising alternative is to utilize recent technological advancements to identify new biomarkers identifying positive cocaine-treatment outcomes. For example, remote physiological monitoring (RPM) via small, discrete devices can allow researchers and clinicians to assess continuous changes in health parameters such as heart rate, respiration, and activity.

In a recently completed study I conducted with collaborators at Baylor College of Medicine, the RPM device BioHarness was used to assess changes in both heart rate and respiration following intravenous (IV) administration of cocaine (40 mg) or placebo among non-treatment seeking, cocaine-dependent individuals in a controlled hospital setting. As expected, significant increases in heart rate were observed over time following cocaine administration compared to placebo. Non-significant changes in respiration were in a similar direction. A benefit of BioHarness was the ability to continuously assess respiration, allowing for a secondary analysis of peak effects. This secondary analysis revealed a significant effect of cocaine on peak respiratory rates relative to placebo. Importantly, heart rate measures obtained from the relatively inexpensive BioHarness device mapped closely to the same measures obtained from standard hospital equipment at periodic time-points. Finally, participants found the device to be comfortable to wear.

Overall, the results of the study showed that the BioHarness is a promising RPM device that can accurately assess exposure to cocaine in the laboratory and may provide additional advantages when compared to standard hospital equipment. These results provide a solid foundation and a feasible methodology for assessing cocaine use in the natural environment and, potentially, detecting health-related improvements resulting from successful treatment of this addiction.

Recent Awards & Honors

Scott Lane
Received the 2014 John P. McGovern Award for Outstanding Teaching from the Graduate School of Biomedical Sciences.

Anka Vujanovic
Received the College on Problems of Drug Dependence Travel Award for Early Career Investigators; Received funding from the Hogg Foundation for Mental Health for her proposal: "Posttraumatic Stress and Distress Tolerance: Associations with Psychiatric Inpatient Treatment."

Margaret Wardle
Received funding from the National Institute on Drug Abuse, 1R03DA036649, for her proposal: "Individual Differences in Motivational Values of Reward Cues."

Thomas Northrup
Appointed Co-Investigator of the Advanced Clinical Design and Statistical Analysis Core P50 component (DA009262 PI: C. Green)

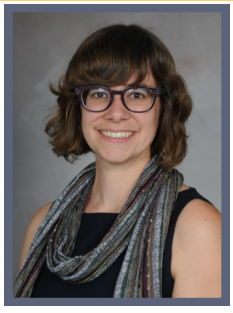
Research Update

2014 Selected **Faculty** Publications

- **Schmitz JM**, **Green CE**, Stotts AL, Lindsay JA, Rathnayaka NS, Grabowski J, Moeller FG: A two-phased screening paradigm for evaluating candidate medications for cocaine cessation or relapse prevention: Modafinil, levodopa-carbidopa, naltrexone. *Drug and Alcohol Dependence, 136,* 100-107, 2014. PMCID: PMC3944935.
- Stotts AL, **Vujanovic A**, Heads A, Suchting R, **Green CE**, **Schmitz JM.** (In Press). Avoidance and inflexibility in characterizing response to contingency management for cocaine use disorders: A secondary profile analysis. *Psychology of Addictive Behaviors*.
- **Lane SD, Green CE, Schmitz JM**, Rathnayaka N, Fang WB, Ferré S, Moeller FG. (In Press). Comparison of caffeine and d-amphetamine in cocaine-dependent subjects: differential outcomes on subjective and cardiovascular effects, reward learning, and salivary paraxanthine. *Journal of Addiction Research and Therapy*.
- Liu S, **Green CE, Lane SD**, Kosten TR, Moeller FG, Nielsen DA, **Schmitz JM**. (In Press). The influence of dopamine beta-hydroxylase gene polymorphism rs1611115 on levodopa/carbidopa treatment for cocaine dependence: A preliminary study. *Pharmacogenetics and Genomics*.
- Dias NR, **Green CE**, Rathnayaka N, **Schmitz JM, & Lane SD**. (In Press). Demographic and psychological factors associated with lifetime cocaine use: An exploratory factor analysis of baseline questionnaires. *Addictive Disorders & Their Treatment*.

CNRA Welcomes New Faculty

Michael Weaver, MD, is Professor and Medical Director of the CNRA. He received his M.D. degree from Northeast Ohio Medical University; completed Residency in Internal Medicine and a Fellowship in Addiction Medicine at Virginia Commonwealth University (VCU) Health System; and is Board-certified in both Internal Medicine and Addiction Medicine. Dr. Weaver has multiple publications in the fields of addiction medicine and pain management. He joined the CNRA in January 2014 and is collaborating with other CNRA researchers on studies involving cocaine, marijuana, and electronic cigarettes.



Margaret Wardle, Ph.D., received her Ph.D. in Clinical Psychology from University of Illinois at Chicago, and then completed a post-doc in human behavioral pharmacology with Dr. Harriet de Wit at University of Chicago. Her research is focused on the role of emotion and motivation in addiction. She conducted the first study of the "reward-enhancing" effects of stimulants in humans, demonstrating that stimulant drugs acutely enhance emotional and motivational responses to non-drug rewards. This may explain why individuals with preexisting "pleasure deficits," such as depression and anhedonia, are particularly vulnerable to stimulant abuse.

Training Leads to Success

The CNRA is committed to the training and career development of the next generation of addiction scientists, educators, and clinicians. Our current trainees are working hard to make strides in substance abuse research. We are extremely impressed with their research accomplishments.

Angela M. Heads, Ph.D., will present her poster, "Family/Social Problems as a Greater Barrier to Treatment Entry for Women than Men" at The College on Problems of Drug Dependence 76th annual meeting on June 14-19, 2014.

Rob Suchting, Ph.D., will be a co-author on a chapter on Bayesian biostatistics, as well as three posters to be presented at The College on Problems of Drug Dependence 76th annual meeting on June 14-19, 2014.

Samet Kose, MD, Ph.D., attended the 6th International Psychiatry and Psychopharmacology Congress in Antalya, Turkey, on April 16-20, 2014, as a guest speaker. He chaired 4 sessions, gave a talk entitled "Neural Substrates of Drug Reward and Addiction: Insights from Neuroimaging," and conducted a workshop on Psychiatric Neuroimaging. Samet gave an addiction talk at the Marmara University Dept of Psychiatry and Pharmacology Joint Meeting on April 21, 2014. Samet also received the APIRE/ Janssen Research Scholar Award. With this award, he attended the 2014, American Psychiatric Association Meeting in New York on May 2-7, 2014 and also participated in a two day workshop as part of APIRE/ Janssen Research Colloquium. Samet also presented "Neural Correlates of Impulsive Aggressive Behavior in Past Alcohol Dependent Subjects" as a poster at the APA's Young Investigator New Research Poster session.

Nilesh Tannu, MD, attended the Society of Biological Psychiatry's 69th annual scientific meeting in May, where he received a plaque for the '2014 Domestic Travel Fellowship Award' and was invited to attend the Junior Investigator Program during the conference. His invited commentary on "Biomarkers in Psychopharmacology: Present and Future" will be published in the American Journal of Psychiatry.

Joseph Alcorn, a graduate student with CNRA, will present his current dissertation data at the International Society for Research on Aggression Meeting held in Atlanta, GA, on July 15-19, 2014.

Nadeeka Dias, Ph.D., successfully defended her dissertation on eye-tracking measures of attentional bias in cocaine-dependent subjects. This summer she will begin a postdoctoral fellowship in substance abuse and neuroimaging at McLean Hospital/Harvard Medical School.

Nuvan Rathnayaka will present his poster, "Posterior Predictive Power: A Decision-Making Tool for Clinical Trial Design" at The College on Problems of Drug Dependence 76th annual meeting on June 14-19, 2014. He was recently accepted to the graduate program in Biostatistics at UNC Chapel Hill.

Samantha Farris, M.A., is a predoctoral clinical trainee from the University of Houston. Her research broadly focuses on the interplay between substance use, emotional processes, and health vulnerabilities. Specifically, her current work using experimental laboratory methodologies is aimed at examining underlying, explanatory mechanisms related to the maintenance of cigarette smoking in the context of anxious arousal.

Kevin Yan is a first year medical student at UT Houston Medical School. He is a recipient of the Saltzberg Research Fellowship and will be working with Dr. Margaret Wardle on a summer research project. His project will use psychophysiological methods to investigate the effect of opiate antagonism on attention to emotional stimuli.

Your Support Is Needed

Contributions to CNRA help advance important research to develop science-based treatments for those who suffer from substance use disorders. Donations can be made to: UTHealth—CNRA, P.O. Box 301413, Dallas, TX 75303 or by calling

(713) 500-5217

Clinical Corner

Trauma and Addiction

"It was a temporary escape from my miserable life"

In this issue of Clinical Corner we interview a former CNRA client and a professional psychologist to gain a two-sided perspective on trauma and addiction – two disorders that are closely linked, highly prevalent, and complex to treat.

"Trisha" is a former participant in the Treatment Research Program at CNRA, and experienced severe physical and emotional spousal abuse for 7 years. She has used cocaine for 20 years, but her addiction worsened during the abuse.

What role did drug use play in your life?

It was an escape. I didn't have to think about what he had done or would do to me. It was a temporary escape from my miserable life.

At what point did you know this drug had a hold on you?

When I started pawning my children's things, electronic things. When I wouldn't even buy food for the kids in the house. When I no longer had my car.

Do you think the trauma you experienced has played a role in your recovery from this substance?

If I hadn't been treated that way or beat up that way- threatened- I wouldn't still be addicted. It's my escape. I try to avoid thinking or talking about what happened.

Have you ever heard of treatment for PTSD and substance use?

No. I wish there was. I also never sought treatment for substance use because I always thought you had to pay for it and go away for months. I just couldn't do that with my kids and when I was working. I couldn't take a rehab vacation.

Would you be interested in treatment for PTSD and substance use if it were offered? How would it be helpful?

Oh yes. I'd be your number one client. Treatment for the trauma would help get rid of my anger and build up my self-confidence. (Pauses) Sorry this is hard to talk about. I don't like to think about what happened. People that have been through trauma want relief and that's what drug use is about. Relief. Maybe treatment could help people find that relief.

Dr. Vujanovic Ph.D., is an Assistant Professor and Director of Psychology Services at the UT-Harris County Psychiatric Center. Her research focuses on examining biopsychosocial mechanisms underlying the comorbidity between PTSD (and other trauma-related psychopathology) and substance use disorders in order to inform the development of novel treatments.

What is posttraumatic stress disorder (PTSD)?

PTSD is a condition that some people develop after experiencing a traumatic event. Symptoms fall into four clusters that last more than one month, and are associated with distress and difficulties functioning in daily life.

First, a person with PTSD might be troubled by intrusive or upsetting memories, thoughts, or dreams about the trauma. Second, they might avoid thinking or talking about the trauma or avoid people, places or situations that remind them of the trauma. Third, this person might also experience more negative emotional states, like anger, guilt, or fear, following the trauma; hold exaggerated negative beliefs about themselves, others or the world; or begin to believe distorted thoughts about the cause or aftermath of the trauma.

For example, they might begin to think, "You can't trust anyone," or "It was all my fault." This person might begin to feel especially detached from others and have difficulty experiencing positive feelings.

Fourth, this person might also have trouble sleeping or concentrating, feel especially irritable or angry, startle easily, engage in reckless or self-destructive behaviors, and be very hypervigilant and on guard.

PTSD might look different from person to person, since each person might experience a different con-

stellation of symptoms at any one time. Clinically, assessment is important, and in the context of treatment, ongoing assessment is key to monitoring changes in symptoms and functioning.

How should clinicians treat SUD in a client who also suffers from PTSD?

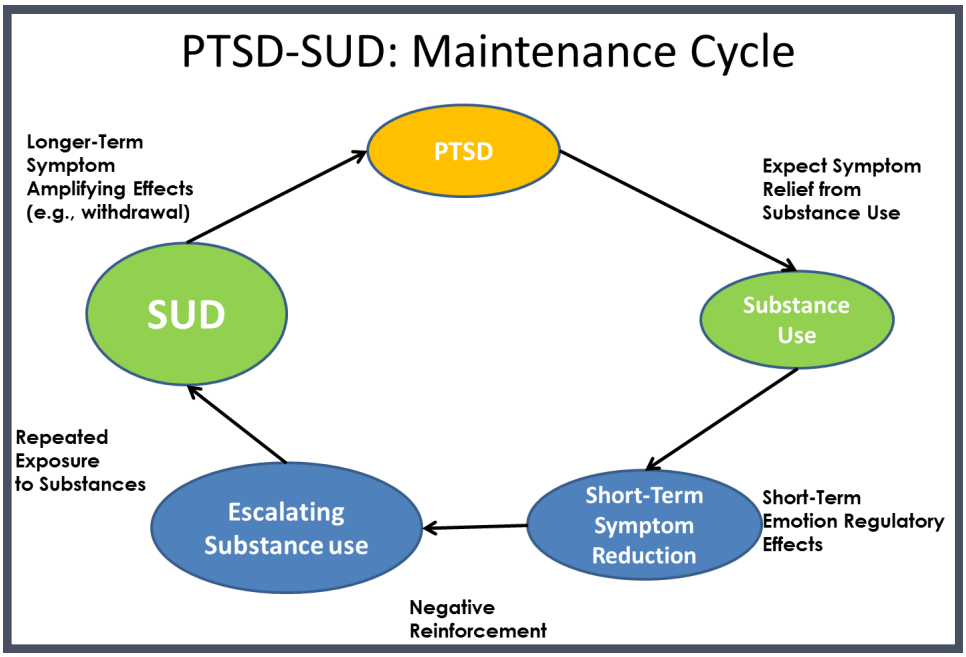
It is important for clinicians treating SUD to be aware of the impact of patients' trauma histories on their current functioning and substance use. Emphasis on screening and assessment of trauma exposure and related symptoms, including PTSD, should be conducted and psychoeducation regarding the associations and implications for substance use provided.

SUD clinicians might find it useful to help patients with PTSD increase emotion regulation skills and adaptive ways of coping. This might be helpful in counteracting the emotion regulatory role that substances have likely played over time.

Appropriate referrals to clinicians specializing in the treatment of traumatic stress or integrated treatment of PTSD-SUD should be made, when appropriate.

If a client uses drugs to "self-medicate" or cope with distressing thoughts about the trauma, will their PTSD symptoms get worse when they stop using drugs?

No. In fact, PTSD symptoms often decrease with abstinence from substances. However, in the absence of adaptive coping skills, even lower levels of PTSD symptoms might be difficult for people in acute recovery to handle, especially since they have been used to abusing substances to cope with, numb out, or escape from difficult emotional states. That is why integrated treatments that address both issues at the same time, concurrently, are so important.



Adapted from Stewart & Conrod (2003)

Often it helps to explain to clients how PTSD and SUD are linked; we call this the "Maintenance Cycle." Because of this linkage, these conditions need to be addressed together. As we know, when you address just one or the other in a person suffering from both, rates of relapse are high and rates of successful PTSD treatment are low.

Does treatment for PTSD involve confronting past trauma events? How does this help?

Yes. Evidence-based treatment of PTSD often does involve processing memories, thoughts, and emotions related to the traumatic event out loud and/or in writing.

Treatment often focuses on processing thoughts and emotions related to the trauma and helping individuals to confront fearful memories and thoughts related to the trauma and create less distressing memories and beliefs. Treatment can also help to create more balanced ways of thinking about the traumatic events and the factors leading up to them or following them. The good news is that PTSD is treatable, and individuals who complete the available, evidence-based treatments for PTSD experience significant symptom relief.

If you suspect that you or someone you know might have PTSD, it is important to seek help from a mental health professional who can evaluate the symptoms and propose a treat-

To participate in one of our ongoing clinical trials for treatment of substance use, call **713-500-DRUG (3784)**

Inside the CNRA

The CNRA currently has three ongoing studies of new medications for substance use disorders.

- **Clinical Trial of Citalopram in Cocaine Dependence**
- **Cognitive-enhancing Dopamine Medications for Cocaine Dependence**
- **PPAR Gamma Agonist Treatment for Cocaine Dependence**

CNRA Program Features:

- No Cost Treatment for Cocaine Dependence
- 100% confidential
- Medical & Behavioral Treatments
- Experienced and Professional Staff
- A Safe and Clean Atmosphere
- Free Parking and Metro Tickets
- Financial Compensation for Research Participation
- Funded by the National Institute on Drug Abuse (NIDA)

Appointments:

713-500-DRUG (3784)

Clinic Hours:
Monday – Friday 7:30-4:00

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Visit us online: http://med.uth.edu/psychiatry/research/addiction